Patent claims

1. Combined use of a pulmonary surfactant and a PDE5 inhibitor for preventing or reducing the onset of symptoms of a disease, or treating or reducing the severity of a disease in a patient in need thereof, in which disease pulmonary surfactant malfunction and/or phosphodiesterase 5 (PDE5) activity is detrimental.

2. Use of a combination of a pulmonary surfactant and a PDE5 inhibitor for the preparation of a medicament for preventing or reducing the onset of symptoms of a disease, or treating or reducing the severity of a disease in a patient in need thereof, in which disease pulmonary surfactant malfunction and/or phosphodiesterase 5 (PDE5) activity is detrimental.

3. Method for preventing or reducing the onset of symptoms of a disease in which pulmonary surfactant malfunction and/or phosphodiesterase 5 (PDE5) activity is detrimental, or treating or reducing the severity of a disease in which pulmonary surfactant malfunction and/or phosphodiesterase 5 (PDE5) activity is detrimental by administering to a patient in need thereof an effective amount of (1) a pulmonary surfactant and (2) a PDE5 inhibitor.

4. The method according to claim 3, wherein an effective amount of (1) a pulmonary surfactant and (2) a PDE5 inhibitor is administered simultaneously to a patient in need thereof.

5. The method according to claim 3, wherein an effective amount of (1) a pulmonary surfactant and (2) a PDE5 inhibitor are administered in succession, close in time or remote in time, in any order whatever to a patient in need thereof.

6. Method for preparing a pharmaceutical composition which is effective for preventing or reducing the onset of symptoms of a disease in which pulmonary surfactant malfunction and/or phosphodiesterase 5 (PDE5) activity is detrimental, or treating or reducing the severity of a disease in which pulmonary surfactant malfunction and/or phosphodiesterase 5 (PDE5) activity is detrimental, which method comprises mixing an effective amount of a pulmonary surfactant and a PDE5 inhibitor with a pharmaceutically acceptable carrier.

7. Use or method according to any of claims 1 to 6, wherein the pulmonary surfactant is selected from the group consisting of PORACTANT ALFA, BERACTANT, BOVACTANT, COLFOSCERIL PALMITATE, SURFACTANT-TA, CALFACTANT, PUMACTANT, LUSUPULTIDE OR SINAPULTIDE.

8. Use or method according to claim 7, wherein the pulmonary surfactant is LUSUPULTIDE.

9. Use or method according to any of claims 1 to 6, wherein the PDE5 inhibitor is selected from
4-Methyl-5-(4-pyridinyl)thiazole-2-carboxamide;
2,2',2",2"'-[(4,8-dipiperidinopyrimido[5,4-d]pyrimidine-2,6-diyl)-dinitrilo]-tetraethanol;
2-(2-propoxyphenyl)purin-6(1H)-one2-(2-propoxyphenyl)-1,7-dihydro-5H-purin-6-one;
1-[6-chloro-4-(3,4-methylenedioxybenzylamino)quinazolin-2-yl]-piperidine-4-carboxylic acid;
(+)-cis-5-methyl-2-[4-(trifluoromethyl)benzyl]-3,4,5,6a,7,8,9-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one;
5-[6-fluoro-1-(phenylmethyl)-1H-indazol-3-yl]-2-furan-methanol;
cis-2-hexyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo-[2,1-b]purin-4-one;
4-(3-chloro-4-methoxybenzylamino)-1-(4-hydroxypiperidin-1-yl)-phthalazine-6-carbonitrile;
(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxy-phenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;
2-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulfonyl)phenyl]-5-methyl-7-propylimidazo[5,1-f][1,2,4]triazin-4(3H)-one;
1-ethyl-4-[[3-[3-ethyl-4,7-dihydro-7-oxo-2-(2-pyridinylmethyl)-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-4-propoxyphenyl]sulfonyl]-piperazine;
2-(2-methylpyridin-4-ylmethyl)-1-oxo-8-(2-pyrimidinylmethoxy)-4-(3,4,5-trimethoxyphenyl)-1,2-dihydro[2,7]naphthyridine-3-carboxylic acid methyl ester;
3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;
1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide;
N-(3,4-dimethoxybenzyl)-2-[2-hydroxy-1(R)-methylethylamino]-5-nitrobenzamide;
5-[2-ethoxy-5-(4-methyl-1-piperazinylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
3-ethyl-8-[2-[4-(hydroxymethyl)piperidin-1-yl]benzylamino]-2,3-dihydro-1H-imidazo[4,5-g]quinazoline-2-thione;
2-(4-aminophenyl)-1-oxo-7-(2-pyridinylmethoxy)-4-(3,4,5-trimethoxyphenyl)-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester;
pentane-1-sulfonic acid [1-[3-(3,4-dichloro-benzyl)-2-methyl-3H--benzoimidazol-5-yl]-methanoyl}-amide;
1-[[3-(7,8-dihydro-8-oxo-1H-imidazo[4,5-g]quinazolin-6-yl)-4-propoxyphenyl]sulfonyl]-4-methylpiperazine;
1-cyclopentyl-6-(3-ethoxy-4-pyridinyl)-3-ethyl-1,7-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulfonyl)-2-[2-methoxy-1(R)-methyl-ethoxy]pyridin-3-yl]-2-methyl-6,7-dihydro-2H-pyrazolo[4,3-d]-pyrimidin-7-one;
2-(1H-imidazol-1-yl)-6-methoxy-4-(2-methoxyethylamino)-quinazoline;
(1Z)-N-benzyl-2-[6-fluoro-2-methyl-3-(3,4,5-trimethoxybenzylidene)-3H-inden-1-yl]-acetamide;
3,6-dihydro-5-(o-propoxyphenyl)-7H-s-triazolo[4,5-d]pyrimidin-7-one; and

3,4-dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-2(1H)-quinolinone, or a pharmaceutically acceptable salt or a N-oxide thereof or a pharmaceutically acceptable salt of the latter.

10. Use or method according to any of claims 1 to 9, wherein the PDE5 inhibitor is selected from
4-Methyl-5-(4-pyridinyl)thiazole-2-carboxamide;
2,2',2'',2'''-[(4,8-dipiperidinopyrimido[5,4-d]pyrimidine-2,6-diyl)-dinitrilo]-tetraethanol;
2-(2-propoxyphenyl)purin-6(1H)-one2-(2-propoxyphenyl)-1,7-dihydro-5H-purin-6-one;
1-[6-chloro-4-(3,4-methylenedioxybenzylamino)quinazolin-2-yl]-piperidine-4-carboxylic acid;
(+)-cis-5-methyl-2-[4-(trifluoromethyl)benzyl]-3,4,5,6a,7,8,9-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one;
5-[6-fluoro-1-(phenylmethyl)-1H-indazol-3-yl]-2-furan-methanol;
cis-2-hexyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo-[2,1-b]purin-4-one;
4-(3-chloro-4-methoxybenzylamino)-1-(4-hydroxypiperidin-1-yl)-phthalazine-6-carbonitrile;
(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxy-phenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;
2-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulfonyl)phenyl]-5-methyl-7-propylimidazo[5,1-f][1,2,4]triazin-4(3H)-one;
1-ethyl-4-[[3-[3-ethyl-4,7-dihydro-7-oxo-2-(2-pyridinylmethyl)-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-4-propoxyphenyl]sulfonyl]-piperazine;
2-(2-methylpyridin-4-ylmethyl)-1-oxo-8-(2-pyrimidinylmethoxy)-4-(3,4,5-trimethoxyphenyl)-1,2-dihydro[2,7]naphthyridine-3-carboxylic acid methyl ester;
3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;
1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide;
N-(3,4-dimethoxybenzyl)-2-[2-hydroxy-1(R)-methylethylamino]-5-nitrobenzamide;
5-[2-ethoxy-5-(4-methyl-1-piperazinylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
3-ethyl-8-[2-[4-(hydroxymethyl)piperidin-1-yl]benzylamino]-2,3-dihydro-1H-imidazo[4,5-g]quinazoline-2-thione;
2-(4-aminophenyl)-1-oxo-7-(2-pyridinylmethoxy)-4-(3,4,5-trimethoxyphenyl)-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester;
pentane-1-sulfonic acid [1-[3-(3,4-dichloro-benzyl)-2-methyl-3H--benzolmidazol-5-yl]-methanoyl}-amide;
1-[[3-(7,8-dihydro-8-oxo-1H-imidazo[4,5-g]quinazolin-6-yl)-4-propoxyphenyl]sulfonyl]-4-methylpiperazine;
1-cyclopentyl-6-(3-ethoxy-4-pyridinyl)-3-ethyl-1,7-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulfonyl)-2-[2-methoxy-1(R)-methyl-ethoxy]pyridin-3-yl]-2-methyl-6,7-dihydro-2H-pyrazolo[4,3-d]-pyrimidin-7-one;
2-(1H-imidazol-1-yl)-6-methoxy-4-(2-methoxyethylamino)-quinazoline;

(1Z)-N-benzyl-2-[6-fluoro-2-methyl-3-(3,4,5-trimethoxybenzylidene)-3H-inden-1-yl]-acetamide; 3,6-dihydro-5-(o-propoxyphenyl)-7H-s-triazolo[4,5-d]pyrimidin-7-one; and 3,4-dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-2(1H)-quinolinone, or a pharmaceutically acceptable salt or a N-oxide thereof or a pharmaceutically acceptable salt of the latter.

11. Use or method according to any of claims 1 to 6, wherein the PDE5 inhibitor is selected from the group of SELECTED PDE5 INHIBITORs.

12. Use or method according to any of claims 1 to 6, wherein the SELECTED PDE5 INHIBITOR is selected from the group consisting of SILDENAFIL, VARDENAFIL or TADALAFIL.

13. Use or method according to any of claims 1 to 12, wherein the SELECTED PDE5 INHIBITOR is selected from the group consisting of SILDENAFIL, VARDENAFIL or TADALAFIL.

14. Use or method according to claim 13, wherein the SELECTED PDE5 INHIBITOR is SILDENAFIL.

15. Use or method according to any of claims 1 to 14, wherein the disease in which pulmonary surfactant malfunction and/or phosphodiesterase 5 (PDE5) activity is detrimental is selected from the group consisting of COPD, bronchitis, bronchial asthma, pulmonary fibroses, emphysema, interstitial pulmonary disorders, pneumonia, ALI, ARDS, IRDS and asthma bronchiale.

16. Pharmaceutical composition suited for the use according to claims 1 and 2, comprising as a fixed combination

(a) an effective amount of a pulmonary surfactant and
(b) an effective amount of a PDE5 inhibitor, and optionally
(c) a pharmaceutically acceptable carrier.

17. Pharmaceutical composition according to claim 16, which is a fixed pharmaceutical composition for intratracheally or intrabronchially instillation.

18. Pharmaceutical composition suited for the use according to claims 1 and 2, comprising as a free combination

(a) an effective amount of a pulmonary surfactant and optionally a pharmaceutically acceptable carrier and
(b) an effective amount of a PDE5 inhibitor and optionally a pharmaceutically acceptable carrier.

19. Pharmaceutical composition according to any of claims 16 to 18, wherein the pulmonary surfactant is selected from the group consisting of PORACTANT ALFA, BERACTANT, BOVACTANT,

COLFOSCERIL PALMITATE, SURFACTANT-TA, CALFACTANT, PUMACTANT, LUSUPULTIDE OR SINAPULTIDE.

20. Pharmaceutical composition according to claim 19, wherein the pulmonary surfactant is LUSUPULTIDE.

21. Pharmaceutical composition according to any of claims 16 to 18, wherein the PDE5 inhibitor is selected from

4-Methyl-5-(4-pyridinyl)thiazole-2-carboxamide;

2,2',2",2"'-[(4,8-dipiperidinopyrimido[5,4-d]pyrimidine-2,6-diyl)-dinitrilo]-tetraethanol;

2-(2-propoxyphenyl)purin-6(1H)-one2-(2-propoxyphenyl)-1,7-dihydro-5H-purin-6-one;

1-[6-chloro-4-(3,4-methylenedioxybenzylamino)quinazolin-2-yl]-piperidine-4-carboxylic acid;

(+)-cis-5-methyl-2-[4-(trifluoromethyl)benzyl]-3,4,5,6a,7,8,9-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one;

5-[6-fluoro-1-(phenylmethyl)-1H-indazol-3-yl]-2-furan-methanol;

cis-2-hexyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo-[2,1-b]purin-4-one;

4-(3-chloro-4-methoxybenzylamino)-1-(4-hydroxypiperidin-1-yl)-phthalazine-6-carbonitrile;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxy-phenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

2-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulfonyl)phenyl]-5-methyl-7-propylimidazo[5,1-f][1,2,4]triazin-4(3H)-one;

1-ethyl-4-[[3-[3-ethyl-4,7-dihydro-7-oxo-2-(2-pyridinylmethyl)-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-4-propoxyphenyl]sulfonyl]-piperazine;

2-(2-methylpyridin-4-ylmethyl)-1-oxo-8-(2-pyrimidinylmethoxy)-4-(3,4,5-trimethoxyphenyl)-1,2-dihydro[2,7]naphthyridine-3-carboxylic acid methyl ester;

3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;

1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide;

N-(3,4-dimethoxybenzyl)-2-[2-hydroxy-1(R)-methylethylamino]-5-nitrobenzamide;

5-[2-ethoxy-5-(4-methyl-1-piperazinylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

3-ethyl-8-[2-[4-(hydroxymethyl)piperidin-1-yl]benzylamino]-2,3-dihydro-1H-imidazo[4,5-g]quinazoline-2-thione;

2-(4-aminophenyl)-1-oxo-7-(2-pyridinylmethoxy)-4-(3,4,5-trimethoxyphenyl)-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester;

pentane-1-sulfonic acid [1-[3-(3,4-dichloro-benzyl)-2-methyl-3H--benzoimidazol-5-yl]-methanoyl]-amide;

1-[[3-(7,8-dihydro-8-oxo-1H-imidazo[4,5-g]quinazolin-6-yl)-4-propoxyphenyl]sulfonyl]-4-methylpiperazine;

1-cyclopentyl-6-(3-ethoxy-4-pyridinyl)-3-ethyl-1,7-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulfonyl)-2-[2-methoxy-1(R)-methyl-ethoxy]pyridin-3-yl]-2-methyl-6,7-dihydro-2H-pyrazolo[4,3-d]-pyrimidin-7-one;
2-(1H-imidazol-1-yl)-6-methoxy-4-(2-methoxyethylamino)-quinazoline;
(1Z)-N-benzyl-2-[6-fluoro-2-methyl-3-(3,4,5-trimethoxybenzylidene)-3H-inden-1-yl]-acetamide;
3,6-dihydro-5-(o-propoxyphenyl)-7H-s-triazolo[4,5-d]pyrimidin-7-one; and
3,4-dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-2(1H)-quinolinone, or a pharmaceutically acceptable salt or a N-oxide thereof or a pharmaceutically acceptable salt of the latter.

22. Pharmaceutical composition according to any of claims 16 to 21, wherein the PDE5 inhibitor is selected from
4-Methyl-5-(4-pyridinyl)thiazole-2-carboxamide;
2,2',2",2"'-[(4,8-dipiperidinopyrimido[5,4-d]pyrimidine-2,6-diyl)-dinitrilo]-tetraethanol;
2-(2-propoxyphenyl)purin-6(1H)-one2-(2-propoxyphenyl)-1,7-dihydro-5H-purin-6-one;
1-[6-chloro-4-(3,4-methylenedioxybenzylamino)quinazolin-2-yl]-piperidine-4-carboxylic acid;
(+)-cis-5-methyl-2-[4-(trifluoromethyl)benzyl]-3,4,5,6a,7,8,9-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one;
5-[6-fluoro-1-(phenylmethyl)-1H-indazol-3-yl]-2-furan-methanol;
cis-2-hexyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo-[2,1-b]purin-4-one;
4-(3-chloro-4-methoxybenzylamino)-1-(4-hydroxypiperidin-1-yl)-phthalazine-6-carbonitrile;
(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxy-phenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;
2-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulfonyl)phenyl]-5-methyl-7-propylimidazo[5,1-f][1,2,4]triazin-4(3H)-one;
1-ethyl-4-[[3-[3-ethyl-4,7-dihydro-7-oxo-2-(2-pyridinylmethyl)-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-4-propoxyphenyl]sulfonyl]-piperazine;
2-(2-methylpyridin-4-ylmethyl)-1-oxo-8-(2-pyrimidinylmethoxy)-4-(3,4,5-trimethoxyphenyl)-1,2-dihydro[2,7]naphthyridine-3-carboxylic acid methyl ester;
3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;
1-(2-chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide;
N-(3,4-dimethoxybenzyl)-2-[2-hydroxy-1(R)-methylethylamino]-5-nitrobenzamide;
5-[2-ethoxy-5-(4-methyl-1-piperazinylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
3-ethyl-8-[2-[4-(hydroxymethyl)piperidin-1-yl]benzylamino]-2,3-dihydro-1H-imidazo[4,5-g]quinazoline-2-thione;
2-(4-aminophenyl)-1-oxo-7-(2-pyridinylmethoxy)-4-(3,4,5-trimethoxyphenyl)-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester;

pentane-1-sulfonic acid [1-[3-(3,4-dichloro-benzyl)-2-methyl-3H--benzolmidazol-5-yl]-methanoyl}-amide;
1-[[3-(7,8-dihydro-8-oxo-1H-imidazo[4,5-g]quinazolin-6-yl)-4-propoxyphenyl]sulfonyl]-4-methylpiperazine;
1-cyclopentyl-6-(3-ethoxy-4-pyridinyl)-3-ethyl-1,7-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulfonyl)-2-[2-methoxy-1(R)-methyl-ethoxy]pyridin-3-yl]-2-methyl-6,7-dihydro-2H-pyrazolo[4,3-d]-pyrimidin-7-one;
2-(1H-imidazol-1-yl)-6-methoxy-4-(2-methoxyethylamino)-quinazoline;
(1Z)-N-benzyl-2-[6-fluoro-2-methyl-3-(3,4,5-trimethoxybenzylidene)-3H-inden-1-yl]-acetamide;
3,6-dihydro-5-(o-propoxyphenyl)-7H-s-triazolo[4,5-d]pyrimidin-7-one; and
3,4-dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-2(1H)-quinolinone, or a pharmaceutically acceptable salt or a N-oxide thereof or a pharmaceutically acceptable salt of the latter.

23. Pharmaceutical composition according to any of claims 16 to 18, wherein the PDE5 inhibitor is selected from the group of SELECTED PDE5 INHIBITORs.

24. Pharmaceutical composition according to any of claims 16 to 18, wherein the SELECTED PDE5 INHIBITOR is selected from the group consisting of SILDENAFIL, VARDENAFIL or TADALAFIL.

25. Pharmaceutical composition according to any of claims 16 to 24, wherein the SELECTED PDE5 INHIBITOR is SILDENAFIL.

26. Use of a pharmaceutical composition according to any of claims 16 to 25 for the treatment of COPD, bronchitis, bronchial asthma, pulmonary fibroses, emphysema, interstitial pulmonary disorders, pneumonia, ALI, ARDS, IRDS or asthma bronchiale.

27. Use of a pharmaceutical composition according to claim 26, wherein the pulmonary surfactant is administered by intratracheal or intrabronchial instillation and the PDE5 inhibitor is administered orally.

28. Use of a pharmaceutical composition according to claim 27, wherein the pulmonary surfactant is LUSUPULTIDE and the PDE5 inhibitor is SILDENAFIL.